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RESEARCH ARTICLE

HPV infection and pre-term birth: a data-linkage study using Scottish Health Data [version 1; peer review: 3 approved]

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Abstract

Background: We aimed to investigate whether infection with high-risk (HR) types of human papilloma virus (HPV) or HPV-associated cervical disease were associated with preterm birth (<37 weeks gestation). In a sub-group of younger women who were eligible for the HPV vaccine, we aimed to determine whether prior vaccination against the specific HPV-types, HPV-16 and -18 modified preterm birth risk.

Methods: This was a data-linkage study, which linked HPV-associated viral and pathological information (from the Scottish HPV Archive) from women aged 16-45 years to routinely collected NHS maternity- and hospital-admission records from 1999–2015. Pregnancy outcomes from 5,598 women with term live birth (≥37 weeks gestation, n=4,942), preterm birth (<37 weeks gestation, n=386) or early miscarriage (<13 weeks gestation, n=270). Of these, data from HPV vaccine-eligible women (n=3,611, aged 16-25 years) were available, of whom 588 had been vaccinated. HPV-associated disease status was defined as: HR HPV-positive no disease, low-grade abnormalities or high-grade disease.

Results: High-grade HPV-associated cervical disease was associated with preterm birth (odds ratio=1.843 [95% confidence interval 1.101–3.083], p=0.020) in adjusted binary logistic regression analysis, in all women, but there were no associations with HR HPV-infection alone or with low-grade abnormalities. No associations between any HPV parameter and preterm birth were seen in vaccine-eligible women, nor was there any effect of prior vaccination.

Conclusions: HPV-associated high-grade cervical disease was associated with preterm birth, but there were no associations with HR HPV-infection or low-grade cervical disease. Thus HPV-infection alone (in the absence of cervical disease) does not appear to be an independent risk factor for preterm birth. For women who have undergone treatment for CIN and become pregnant, these results demonstrate the need to monitor for signs of preterm birth.

Open Peer Review

Reviewer Status

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Keywords

Pregnancy, Preterm Birth, Human Papilloma Virus, Cervix, Data linkage

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Introduction

Human papillomavirus (HPV) is a sexually transmissible virus that infects cervical cells. Normally, the virus is cleared by the immune system, becoming undetectable within two years¹. Persistent HPV infection causes pre-cancerous cervical intraepithelial neoplasia (CIN); left untreated, CIN can develop into cervical cancer². Over 200 HPV types exist, of which 14 are oncogenic or high-risk (HR). Two such HR types, HPV-16 and -18, are responsible for 70–80% of invasive cervical cancers³. Treatment of CIN and cervical cancer is by removal of the abnormal cervical cells⁴.

The cervix is important for maintenance of pregnancy, with barrier and immune mechanisms that protect the growing foetus⁵. HPV-infection may alter cervical function, possibly increasing the risk of intrauterine infections⁶ and subsequent complications such as preterm birth⁷ or miscarriage⁸.

The relationships between HPV infection and pregnancy outcomes are unclear. Some studies have shown no association^{9,10}, whereas others have suggested that HPV-infection, cervical disease and/or its treatment are associated with adverse pregnancy outcomes, such as miscarriage¹¹, premature preterm rupture of membranes (PPROM)¹² or spontaneous preterm birth^{13,14}.

We performed a data-linkage cohort study, linking women with HPV viral and pathological data with their own pregnancy records. The aims for this study were to determine whether HR HPV-infection, specific HR HPV types, or the presence of HPV-associated cervical disease were associated with preterm birth (<37 weeks gestation), early miscarriage (<13 weeks gestation) or stillbirth (pregnancy loss at ≥24 weeks gestation) and whether previous vaccination against HPV-16/18 affected these outcomes.

Methods

Study background

This study was a data-linkage study, linking data from women with HPV viral and pathological data contained within the Scottish HPV Archive (see below) with their own pregnancy records. After data-cleaning, the retrospective data from the women in the resulting cohort were analysed for associations between the HPV viral/pathology parameters and adverse pregnancy outcomes: preterm birth (<37 weeks gestation), early miscarriage (<13 weeks gestation) and stillbirth (≥24 weeks gestation). The study population for whom data were obtained and linked were women who had samples and data within the Scottish HPV Archive and who had had details of pregnancy outcomes.

Eligibility criteria

Women whose HPV-infection status was known at the time of birth were included. As HPV is usually cleared within 2 years¹ and women are advised to delay their next scheduled cervical smear until at least 12 weeks postnatally⁴, women who had a pregnancy up to 1 year prior to the cytology date were also included. In women who had had more than one pregnancy, the pregnancy outcome nearest the cytology date was included.

Exclusion criteria for the study were: Multiple (twin) pregnancies, as these babies are more often routinely delivered preterm; therapeutic terminations, ectopic pregnancies and trophoblastic disease were also excluded.

Definition of terms

The definitions for pregnancy outcomes were: *Term live births* were women who had a live birth at term (≥37 weeks gestation); *All preterm births* were women with births before 37 weeks' gestation including miscarriages of ≥13 weeks gestation; *Spontaneous preterm births* were women with births prior to 37 weeks' of gestation, including those with PPROM and miscarriages of ≥13 weeks gestation, but excluding iatrogenic preterm births (those delivered by elective caesarean section or those which were induced); *Early Miscarriage* was any spontaneous pregnancy loss before 13 weeks' gestation; *Stillbirth* was defined as any pregnancy loss after 24 weeks' gestation.

Sources of patient information used for the data-linkage

Scottish HPV Archive. Scotland has a cervical screening programme with population coverage of around 70%¹⁵. Until June 2016, women aged 20–60 years were screened; thereafter the age-range was 25–65 years. In September 2008, a routine, school-based HPV vaccination programme for girls aged 11–13 years was introduced, with a “catch-up” immunisation programme for girls aged 13–17 years¹⁶. In 2009, the Scottish HPV Archive was established as a biobank for HPV-associated research. It is a collection of collections which includes residual cervical samples from women attending routine cervical screening and colposcopy clinics, from the year 2000 to the present. Many samples within the Archive have a patient identifier (community health index [CHI] number) and associated clinical, cytology and histology results, obtained from the Scottish Cervical Cytology Recall System (SCCRS). SCCRS is the national IT system that supports the Scottish cervical screening program and contains a woman's entire screening record⁴. A number of samples in the Archive are annotated with HPV status as a consequence of immunisation surveillance and specific research projects^{17,18}, using different HPV assays depending on the nature and objectives of the research projects (Table 1). At the time of data-linkage the Scottish HPV archive contained 31,320 records from women (aged 20–60 years). The Scottish HPV Archive has generic Research Tissue Bank approval from the East of Scotland Research Ethics Service (REC Ref 11/AL/0174) and is registered with Lothian NRS Bioresource. Approval for use of HPV data was given by the Archive Steering Committee (HPV Archive Application Ref 0018).

Scottish Morbidity Record (SMR)02. SMR02 is the Maternity Inpatient and Day Case Dataset¹⁹, held by the Information Services Division (ISD) of the National Health Service (NHS) National Services Scotland (NSS) and covers maternity admissions in Scotland. SMR02 includes over 98% of deliveries, as less than 2% of deliveries occur at home. A quality assurance audit of SMR02 showed that accuracy of the records exceeded 90%, when compared with corresponding written medical records²⁰.

Table 1. Variable coding obtained or used for coding data. Table shows the variables obtained from the data linkage, the source of the data, the codes (ICD or otherwise) used in the original dataset and the codes used for each variable in the data analysis.

Variable name	Description and/or codes received from data sources	Source	Cleaning strategy and coding used
Unique ID	Unique identifier for mother used to link datasets		No change
Maternal age	Maternal age at pregnancy admission (years)	SMR02/ SMR01	No change
Year & month of outcome	Yyyymm	SMR02 / SMR01	No change. Used to calculate time between HPV cytology and pregnancy
Outcome of pregnancy	1=Live birth 2=Still birth 3=Livebirth dying within the first 6 days (early neonatal death) 4=Livebirth dying between 7th completed day and 28th day (late neonatal death) 5=Livebirth dying between 28th day and end of the first year of life (post-neonatal death)	SMR02 / SMR01	0=Term live birth (live birth ≥ 37 weeks) 1=Preterm birth (live birth < 37 weeks); includes late miscarriages (≥13 weeks gestation) 2=Stillbirths – removed 3=Neo-/post-natal death included in live birth data of appropriate gestation 4=Miscarriage. Miscarriages from SMR01 coded as <13 weeks gestation (early); miscarriages from SMR02 were coded as early (<13 weeks) or late (≥13 weeks) by gestation 5=live birth of unknown gestation – removed
Estimated Gestation	Estimated gestation at abortion or delivery (weeks) [not available for data from SMR01]	SMR02 only	Estimated gestation used to define pregnancy outcomes
Miscarriage Flag	Derived from ICD10 coding O01–O03,O05,O06, Type of Abortion, and Outcome of Pregnancy	SMR01 / SMR02	0=No 1=Yes
Type of abortion	1=spontaneous / incomplete abortion (miscarriage) 2=missed abortion (miscarriage) 3=trophoblastic disease 4=therapeutic abortion 5=suspected illegal abortion 6=ectopic pregnancy 8=other abortion 9=unspecified	SMR02	Only present when no live birth Any pregnancies with 1 or 2 classed as miscarriage. For values 3–9, records relating to that pregnancy were removed. Coded as miscarriage: 0=No 1=Yes
Mode of delivery	0=Normal, spontaneous vertex, vaginal delivery, occipito-anterior 1=Cephalic vaginal delivery, with abnormal presentation of the head at delivery, without instruments, with or without manipulation 2=Forceps, low application, without manipulation, forceps delivery NOS 3=Other forceps delivery. Forceps with manipulation, high forceps, mid forceps 4=Vacuum extraction ventouse 5=Breech delivery, spontaneous assisted or unspecified partial breech extraction 6=Breech extraction, NOS 7=Elective (planned) Caesarean Section 8=Emergency / unspecified caesarean section 9=Other and unspecified method of delivery Additional codes provided were from SMR02 coding sheet: A=mid cavity forceps B=rotational forceps C=Ventouse no rotation specified D=Ventouse with rotation E=Other forceps delivery	SMR02	Coding collapsed to: 0=any vaginal delivery 1=any forceps delivery 2=any ventouse delivery 3=any breech delivery 7=Elective caesarean section (ELCS) 8=Emergency caesarean section (EmCS) 9=Missing Coding used to determine whether delivery was by elective caesarean section

Variable name	Description and/or codes received from data sources	Source	Cleaning strategy and coding used
Induction of labour	0=none 1=Artificial rupture of membranes (ARM) 2=Oxytocics 3=ARM + Oxytocics 4=Prostaglandins (includes cervical priming) 5=ARM + Prostaglandins 6=Prostaglandins + Oxytocics 7=Prostaglandins + ARM + Oxytocics 8=Other 9=Not Known	SMR02	0=None 1=ARM only 2=Any drugs ± ARM 9=Missing Coding used to define whether labour onset was spontaneous.
Prelabour rupture of membrane (PROM)	Derived from ICD10 code O42.	SMR02	0=No 1=Yes 99=Missing Coding used for spontaneous labour onset in preterm birth
Ethnicity	A - White (1A=Scottish, 1B=Other British, 1C=Irish, 1K=Gypsy, 1L=Polish, 1Z=other) B- Any mixed or multiple ethnic groups C - Asian (Pakistani / Indian / Bangladeshi / Chinese / Other) D - African E - Caribbean or Black F - Other Ethnic group G - Refused 98= Not given by patient H - 99 = unknown	SMR02 / SMR01	Recorded for approximately 70% of cases only Collapsed to Ethnicity code: 1=White 2=Other 99=Missing
Scottish Index of Multiple Deprivation (SIMD)	SIMD (National quintiles and deciles) SIMD provided from 2004, 2006, 2009, 2012 for each admission. SIMD scores have changed calculation methods and coding direction over time	SMR02 / SMR01	SIMD quintile for 2009 (midpoint between 2000 and 2015) was used for all records. Quintiles were combined as: 1 and 2=most deprived 3, 4 and 5 =least deprived 99=missing
Parity	0-7=number of actual events 8=8 or more actual events 9=not known Not available for SMR01. Some information if patient had another pregnancy	SMR02	0=non-parous 1=parous 99= missing
Smoking history at booking	0=never smoked 1=current smoker 2=former smoker 9=unknown/missing	SMR02	No change
Current Smoking during pregnancy	0=No 1=Yes 9=Unknown/missing	SMR02	No change
Diabetes	1=yes pre-existing (diagnosed before pregnancy) 2=yes gestational (diagnosed during pregnancy) 3= yes time of diagnosis unknown 4=no diabetes during pregnancy 9=not known	SMR02	0=No diabetes 1=any diabetes during pregnancy 9=Missing
Hypertensive disorder in pregnancy	Did not distinguish between pre-existing and gestational hypertension 0=No 1=Yes 99=unknown	SMR02	0=No 1=Yes 99=Missing

Variable name	Description and/or codes received from data sources	Source	Cleaning strategy and coding used
Date of Sample Collection	Date of collection Same as cytology date	HPV Archive	Year only Coded as January of year if no cytology date
Cytology date	Year and month	HPV Archive	Cytology date used to define date of HPV diagnosis Used to calculate time between cytology and pregnancy outcome
Years between cytology and pregnancy	Derived parameter	--	Calculated time between cytology and pregnancy (years). Includes cytology up to a year after pregnancy
HR HPV type	HPV types were detected. For some samples, multiple strains were detected. All positive results denote high-risk (HR) type. HR types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. Some results given as "other HR HPV". Low risk (LR) types were only detected in samples that were specifically genotyped and classed as HR HPV negative. LR types: 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73, 81. HR HPV assays used were Hybrid Capture 2 (Qiagen, Germany), Optiplex HR HPV test (Diamex, Germany), RealTime HR HPV assay (Abbott Molecular, USA), in house PCR assay ²¹ or Linear Array HPV genotyping test (Roche, USA). Assays for individual genotypes used Optiplex HR HPV test, RealTime HR HPV assay or Linear Array HPV genotyping test.	HPV Archive	Coded as : 0=HR HPV negative 1=HPV HR positive 9=HPV unknown If no genotype given but was positive, sample coded as HR HPV. If only LR genotypes present, sample was coded HR HPV negative For specific analysis of HPV 16/18 types, only those samples were used which had a known specific HPV type, coded as: 0=HR HPV negative 1= HPV 16/18 +ve: samples contained either or both of these types, regardless of other types contained therein. 2= non-16/non-18 HR types: samples contained known HR HPV types but not HPV-16 nor HPV-18
Cytology result	Old Codes: (before 2012) • Normal • Borderline squamous changes, mild dyskaryosis • Moderate dyskaryosis, severe dyskaryosis • Unknown	HPV Archive	Data arrived as mix of new and old codes. New codes used, corresponding to old codes as shown Used to define HPV disease
Histology date	Year and month	HPV Archive	No change
Histology result	Samples for histology only taken if abnormal cytology Normal, Cervical intraepithelial neoplasia (CIN) CIN1-3, Cervical glandular intraepithelial neoplasia (CGIN), high-grade dysplasia, high/low-grade intraepithelial lesion, human papilloma virus, squamous cell cancer (SCC), unsatisfactory Available for ~5% of women	HPV Archive	Coded as: 0=Normal, mild changes (HPV), unsatisfactory 1=CIN1, low-grade intraepithelial lesion, changes consistent with HPV 2=CIN2, CIN3, high-grade intraepithelial lesion, SCC, CGIN Used to define HPV disease
HPV-associated cervical disease	Derived parameter based on all HPV data and used as an HPV parameter in analysis.	--	0=HPV Neg/LR 1=HPV HR type, normal cytology 2=Low-grade disease (abnormal cytology: normal/low grade histology, CIN1) 3=High-grade disease (High grade dysplasia, CIN2, CIN3, CGIN, SCC, high-grade intraepithelial lesion) 8=HPV HR type, cytology unknown } marked as 9=HPV disease unknown } missing
HPV vaccination status	Vaccine-eligible women were those who were aged 12 from 2008 onwards, or girls up to 18 years of age who were eligible for the catch-up vaccination programme.	HPV Archive	0=Vaccine-eligible women who were not vaccinated 1=Vaccine-eligible women who were vaccinated 2= Women too old to be eligible for vaccine } marked as missing 9= Eligible women unknown if vaccinated } in VE analyses

SMR01. SMR01 is the General/Acute Inpatient and Day Case Dataset, held by NHS NSS ISD, and covers hospital admissions in Scotland¹⁹. Audit of SMR01 found that accuracy of clinical data was more than 89%, when compared with written medical records²². Miscarriage data were obtained from both SMR01 and SMR02. If an SMR01 record had no corresponding SMR02 record, we assumed that the miscarriage occurred before 13 weeks' gestation, as it is usual practice for pregnancies to be registered on SMR02 before 13 weeks gestation²³. Scottish birth statistics from the Scottish population, obtained from SMR02 and SMR01, are available from the NHS NSS ISD website, Births in Scottish Hospitals²³.

Miscarriage may occur before the mother is aware she is pregnant, and is often managed in an outpatient or general practice setting^{23,24}; such cases would not generate a hospital or maternity record. Women admitted to a hospital ward via an emergency or gynaecology department or early pregnancy unit generate an SMR01 record; women admitted to a maternity unit generate an SMR02 record. Between 1998 and 2016, the population rate of miscarriages managed in Scottish hospitals (data from SMR01 and SMR02) fell from 7.0 to 4.4 per 1000 women aged 15–44 per year²³. From these numbers, the percentage of miscarriages in the Scottish birth data for each year was calculated as:

$$\text{Percentage of miscarriages} = \frac{\text{Number of miscarriages given for each year}}{\text{Number of miscarriages} + \text{number of births for each year}}$$

From this calculation, for the years 1998–2016 the percentage of miscarriages approximated to 8.0–12.0% of all births per year.

National Records of Scotland (NRS). This resource holds the records of stillbirths and infant deaths in Scotland²⁵.

Approval for use of data

Approval for use of NHS NSS and NRS data was obtained from the NHS Privacy Advisory Committee (PAC 74/14). Approval for linkage of previous unlinked datasets was given by the NHS Scotland National Caldicott Guardian Forum (Ref 2015-19). The linked dataset was analysed within the NHS National Safe Haven, provided by NHS Research Scotland²⁶. The Safe Haven is a remote server through which the researcher accesses the health data and services to enable research while protecting the confidentiality of the data. Data remains under the control of the NHS and complies with legislative and NHS policies. The linked dataset is archived within the Safe Haven and is available by application to NHS Scotland via the electronic Data Research and Innovation Service (eDRIS)²⁷, within the Farr Institute for Health Informatics Research.

Data extraction

The data-linkage and -cleaning processes are summarised in Figure 1. Data were transferred between the Scottish HPV Archive and eDRIS, where data-linkage was performed. From all the women's records within the Scottish HPV Archive (N=31,320), those who had had pregnancies recorded in SMR02, SMR01 and NRS were identified by the CHI number. Coded identification

numbers of women with pregnancy records were sent back to the Scottish HPV Archive (n=10,572), from where HPV-genotype, cytology date and result, histology date and result, vaccination date and dosage were collated. These data are denoted as 'HPV viral/pathology data'. The HPV viral/pathology data and corresponding SMR02, SMR01 and NRS records were collated, anonymised and placed in the Safe Haven. For data cleaning and analysis, only the Safe Haven and the linked datasets were accessed.

Pregnancy admission records from SMR02, SMR01 and NRS records for women in the Scottish HPV Archive were received from January 1981 to August 2015. Many of the older women within the Scottish HPV Archive had their pregnancies before their HPV-infection status was known and so were excluded. Records in the Scottish HPV Archive started in 2000, so pregnancy admissions before 1999 were removed; therefore, the time-period for this study was 1999–2015. Duplicate records were removed. Information from multiple admissions per pregnancy outcome were condensed into one record. The variables obtained from SMR01, SMR02, NRS records and the Scottish HPV Archive are presented in Table 1, together with details of data coding and cleaning. Pregnancy records were coded without reference to HPV-infection status. The proportions of women with specific pregnancy outcomes within our final cohort was compared with that of the Scottish population²³ to determine how representative our cohort was of the Scottish population.

Classification of individuals within the dataset

HPV-infection status of each woman was defined as *HR HPV-positive* if there was a positive result for at least one HR HPV type (Table 1). Infections with a mixture of HPV types were common. Low-risk HPV-positive samples (Table 1) and HPV-negative results were considered *HR HPV-negative*.

Women were classed as *HPV-16/18-positive* if they had samples containing HPV-16 and/or HPV-18, irrespective of other types present. Women were classed as *non-16/non-18 HR HPV-positive* if they had samples that were negative for HPV-16 or HPV-18 but contained other known HR HPV types.

HPV-associated cervical disease was classed as: HR HPV-negative; HR HPV-positive no disease (i.e. normal cytology); low-grade abnormalities (borderline/mild dysplasia, normal/low-grade histology, CIN1) or high-grade disease (high-grade dysplasia, CIN2, CIN3, CGIN, cancer, high-grade intraepithelial lesion).

HPV vaccination status. Some women had received the bivalent HPV vaccine¹⁷ (1–3 doses) against HPV-16 and -18. Vaccine-eligible women were classified as: those who had been vaccinated, those eligible (by age) but unvaccinated, or those eligible but whose vaccination status was unavailable; women born before 1990 were too old to have been eligible for vaccination.

Scottish National guidelines require over 90% of women with HPV-associated high-grade cervical disease to have undergone

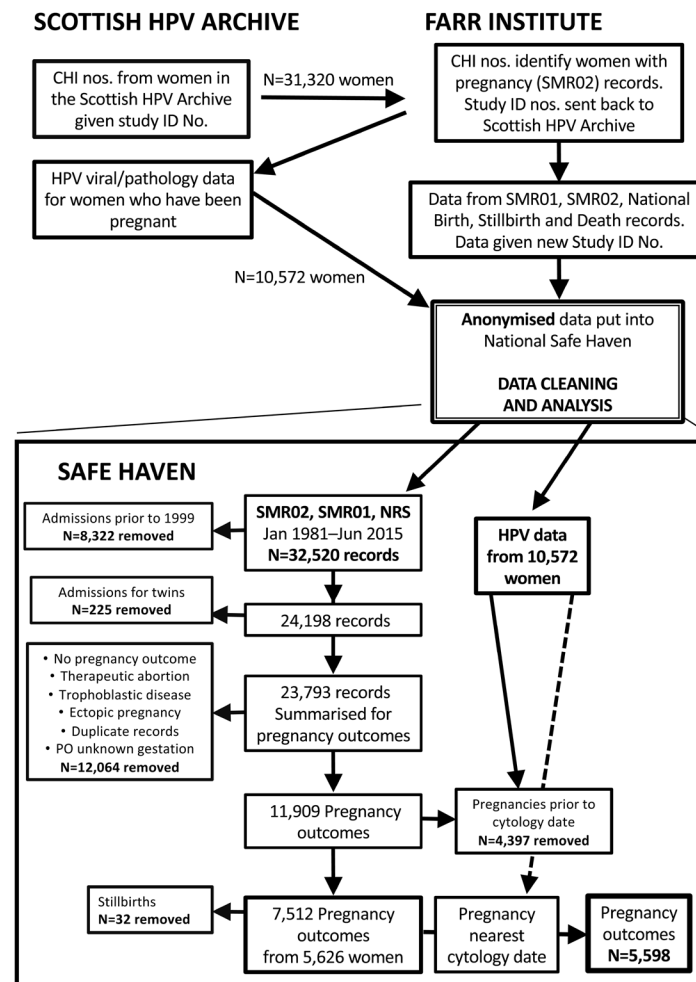


Figure 1. Summary of data-linkage and -cleaning processes.

excisional treatment⁴, but data for the specific treatments used were not available.

Determining cohort reliability

To determine how representative our cohort was of the Scottish population, the proportions of women with specific HPV viral/pathology parameters within our final cohort, were compared with a recent HPV prevalence study in women attending screening in Scotland²⁸, as HPV results are not recorded as part of routine cervical screening. Pathology data (low- and high-grade disease) were compared with data from ISD²⁹.

Potential confounders for pregnancy outcomes were obtained from SMR02 and SMR01: ethnicity, parity, Scottish Index of Multiple Deprivation (SIMD), smoking history and during current pregnancy, diabetes (pre-existing and gestational) and hypertension (any). Coding and definitions for these variables are shown in Table 1. Continuous variables obtained were maternal age and maternal BMI. Neither variable was normally distributed, nor was any transformation able to normalise the

data. Maternal age (range 16–45 years) was severely skewed, with 62.9% of women in our cohort aged <25 years. As we wished to investigate the effects of vaccination, and the vaccine-eligible women were aged <25 years, we chose 20 years as the age cut-off point for the analyses, comparing those aged <20 years with those >20 years. Maternal BMI data were categorised: underweight (BMI <19.9), normal (BMI 20.0–24.9), overweight (BMI 25.0–29.9) and obese (BMI ≥30.0).

Statistical analysis

All statistical analyses were carried out using SPSS v22 (© IBM Corporation, USA). Missing data analysis (Table 2) of the cleaned full dataset was carried out using the ‘Multiple Imputation’ function, which runs regression models of existing data to replace missing data: i.e. the programme looks at patterns of the data available and makes probability judgements (imputations) to give estimates of the missing data. Data was missing for Scottish Index of Material Deprivation (SIMD), ethnicity, parity, hypertensive disorder, current smoking, smoking history, diabetes and maternal BMI (Table 3). Variables were imputed

Table 2. Missing data analysis. Table shows the results of the missing data analysis (number of valid variables, number and percent missing variables) for all variables with missing data.

Variables with missing data	Valid		Missing		Total N
	N	Percent	N	Percent	
No. cases with complete data	3,123	55.8%	2,475	44.2%	5,598
No. individual data values	39,590	88.4%	5,194	11.6%	44,784

Table 3. Imputation models used. Table shows the models used for imputation of the missing data. Data that were not imputed were Pregnancy outcomes as these were the primary outcomes; HPV viral/pathological data because these were the primary factors of interest; maternal age was complete.

Parameters for which missing data was imputed	Valid N	Missing		Imputed values	Model	
		N	Percent		Type	Effects
SIMD	5,562	36	0.6%	180	Logistic Regression	Parity, Hypertensive disorder, Current smoking, Smoking History, Diabetes, Ethnicity, Maternal BMI
Parity	5,504	94	1.7%	470	Logistic Regression	SIMD, Hypertensive disorder, Current smoking, Smoking History, Diabetes, Ethnicity, Maternal BMI
Maternal hypertension	5,484	114	2.0%	570	Logistic Regression	SIMD, Parity, Current smoking, Smoking History, Diabetes, Ethnicity, Maternal BMI
Current Smoking	5,226	372	6.6%	1,860	Logistic Regression	SIMD, Parity, Hypertensive disorder, Diabetes, Ethnicity, Maternal BMI
Smoking history	5,061	537	9.6%	2,685	Logistic Regression	SIMD, Parity, Hypertensive disorder, Current smoking, Diabetes, Ethnicity, Maternal BMI
Maternal diabetes	4,763	835	14.9%	4,175	Logistic Regression	SIMD, Parity, Hypertensive disorder, Current smoking, Smoking History, Ethnicity, Maternal BMI
Maternal BMI at booking (kg/m ²)	4,148	1,450	25.9%	7,250	Linear Regression	SIMD, Parity, Hypertensive disorder, Current smoking, Smoking History, Diabetes, Ethnicity
Ethnicity	3,842	1,756	31.3%	8,780	Logistic Regression	SIMD, Parity, Hypertensive disorder, Current smoking, Smoking History, Diabetes, Maternal BMI

together so that any potential interactions could be taken into account³⁰. For the logistic regression analyses, pooled results from five imputations are presented in the results. The HPV viral/pathology parameters (HR HPV, HPV-16/18 genotype, HPV-associated cervical disease and HPV vaccination status) were not imputed, as these were the primary predictive factors of interest for the analyses.

The proportions of maternal characteristics according to pregnancy outcomes or according to HPV viral/pathology parameters were compared by chi squared or Fisher's exact test analysis and are shown in Table 4 and Table 5, respectively. Binary logistic regression analysis was used for each pregnancy outcome, with women who had had term live births as the comparator group and each HPV viral/pathology parameter as the

predictive factor under analysis. Odds ratios (OR) and 95% confidence intervals (CIs) are presented from unadjusted and adjusted models in all women. To investigate the effects of prior HPV vaccination, the models were run in vaccine-eligible women, with and without vaccination status included. Adjusted models used the imputed dataset and adjusted for maternal factors that might affect pregnancy outcomes: ethnicity, SIMD, parity, age, BMI, diabetes, hypertension and current smoking.

Results

Cohort screening, selection and characteristics

Pregnancy admission records (N=32,520) were received for women who had been pregnant and had HPV viral/pathology data in the Scottish HPV Archive (N=10,572). After data-cleaning and exclusions, we had obtained 7,512 pregnancy

Table 4. Maternal characteristics (original/imputed data) by pregnancy outcome: Term live birth and Any preterm birth. Table shows the numbers and percentages of women in each pregnancy outcome group compared by maternal factors that might affect pregnancy outcome. The numbers shown are from original data or the imputed data (in italics). Term live births (≥ 37 weeks gestation) were compared with any preterm birth (PTB, < 37 weeks gestation). The original (unimputed) data is presented alongside the pooled imputed data (*italics*) to show that the proportions of each parameter are similar between the original and imputed datasets, and the imputation process did not adversely skew the data. P values denote results from chi squared analysis of the pooled imputed data for each parameter between the two groups. Significant p values are highlighted (bold); ns denotes not significant.

Maternal Factor	Original data*		Pooled imputed data†		P value
	Term live births, n (%)	Any PTB, n (%)	Term live births (N=4,942), n (%)	Any PTB (N=386), n (%)	
Age (years)‡					
Mean age (range)	25 (16–45)	24.6 (17–43)	25 (16–45)	24.6 (17–43)	
≤ 20 years	1082 (21.9)	80 (20.7)	1082 (21.9)	80 (20.7)	0.654
> 20 years	3860 (78.1)	306 (79.3)	3860 (78.1)	386 (79.3)	
Ethnicity					
White	3283 (98.1)	267 (97.4)	4838 (97.9)	377 (97.7)	0.713
Other	64 (1.9)	7 (2.6)	104 (2.1)	9 (2.3)	
Parity					
Non-parous	3239 (65.9)	259 (67.4)	3256 (65.8)	261 (67.6)	0.504
Parous	1679 (34.1)	125 (32.6)	1686 (34.1)	125 (32.3)	
SIMD 					
Most deprived	2464 (50.1)	208 (54.3)	2480 (50.2)	211 (54.7)	0.091
Least deprived	2446 (49.9)	175 (45.7)	2462 (49.8)	175 (45.3)	
BMI¶ (kg/m²)					
≤ 19.9 (underweight)	425 (11.0)	47 (17.2)	593 (11.9)	61 (15.8)	0.146
20.0–24.9 (healthy)	1639 (42.5)	115 (42.1)	1981 (40.1)	152 (39.4)	
25.0–29.9 (overweight)	1043 (27.1)	57 (20.9)	1387 (28.1)	97 (25.1)	
≥ 30 (obese)	745 (19.3)	54 (19.8)	981 (19.9)	76 (19.6)	
Current Smoking					
No	3503 (74.1)	235 (64.7)	3642 (73.7)	252 (65.3)	<0.001
Yes	1226 (25.9)	128 (35.3)	1300 (26.3)	134 (34.7)	
Diabetes#					
No	4282 (98.5)	312 (95.7)	4863 (98.4)	370 (95.9)	
Any	64 (1.5)	14 (4.3)	79 (1.6)	16 (4.1)	0.002
Hypertension**					
No	4563 (92.3)	346 (89.6)	4562 (92.3)	346 (89.6)	0.063
Yes	379 (7.7)	40 (10.4)	380 (7.7)	40 (10.4)	

*For the original data, due to missing values, numbers and percentages for each maternal parameter relate to the numbers in each analysis and do not add up to the total number of each pregnancy outcome.

†Imputed data are the pooled results of five imputations. The numbers and percentages presented are representative of the population as a whole and represent the estimated values that would have been obtained had the dataset been complete. Imputed data were used in the logistic regression models.

‡Maternal age was complete. Age range of women in each group is shown.

§Scottish Index of Material Deprivation (SIMD) quintiles were combined as most deprived (quintiles 1 & 2) vs. least deprived (quintiles 3–5).

¶Body mass index (BMI) was calculated as weight (kg) divided by the square of the patient's height (m²)

#Diabetes includes gestational diabetes and pre-existing diabetes (Table 1).

**Hypertension did not distinguish between pre-existing or gestational hypertension within SMR02 (Table 1)

Table 5. Maternal characteristics and HPV viral/pathology parameters in the cohort of women. Table shows the numbers and percentages of maternal characteristics and HPV viral/pathology parameters in the whole cohort of women, compared by Chi Square or Fisher's Exact test. P values from results showing significant differences are highlighted in bold.

Maternal Characteristic [†]	HPV viral/pathology parameter [*]											
	HR HPV (N=4061)			HR HPV Type (N=3519)			HPV-associated cervical disease (N=3884)					
	Negative, n (%)	Positive, n (%)	P value	Negative, n (%)	HPV16/18, n (%)	non-16 /non-18 HR HPV, n (%)	P value	HPV negative, n (%)	HR positive no disease, n (%)	Low-grade abnormalities, n (%)	High-grade disease, n (%)	P value
Age (years)[‡]												
<20 years	666 (16.4)	347 (8.5)	0.024	666 (18.9)	122 (3.5)	111 (3.2)	0.211	623 (16.0)	95 (2.4)	208 (5.4)	23 (0.6)	<0.001
>20 years	1883 (46.4)	1165 (28.7)		1883 (53.5)	420 (11.9)	317 (9.0)		1751 (45.1)	360 (9.3)	685 (17.6)	139 (3.6)	
Ethnicity[§]												
White	2492 (61.4)	1494 (36.8)	0.017	2492 (70.8)	535 (15.2)	425 (12.1)	0.052	2319 (59.7)	448 (11.5)	884 (22.8)	159 (4.1)	0.097
Other	57 (1.4)	18 (0.4)		57 (1.6)	<10 (<0.3)	<10 (<0.3)		55 (1.4)	<10 (<0.3)	<10 (<0.3)	<10 (<0.3)	
Parity												
Non-parous	1752 (43.1)	1018 (25.1)	0.353	1752 (49.8)	390 (11.1)	310 (8.8)	0.139	1652 (42.5)	311 (8.0)	593 (15.3)	84 (2.2)	<0.001
Parous	797 (19.6)	494 (12.2)		797 (22.6)	152 (4.3)	118 (3.3)		722 (18.6)	144 (3.7)	300 (7.7)	78 (2.0)	
SIMD												
Most deprived	1248 (30.7)	818 (20.1)	0.002	1248 (35.5)	313 (8.9)	238 (6.8)	<0.001	1161 (29.9)	226 (5.8)	464 (11.9)	88 (2.3)	0.292
Least deprived	1301 (32.0)	694 (17.1)		1301 (36.9)	229 (6.5)	190 (5.4)		1213 (31.2)	229 (5.9)	429 (11.0)	74 (1.9)	
BMI[¶] (kg/m²)												
<19.9	327 (8.1)	209 (5.1)		327 (9.3)	75 (2.1)	70 (2.0)		308 (7.9)	53 (1.4)	127 (3.3)	13 (0.3)	
20.0–24.9	969 (23.9)	614 (15.1)	0.122	969 (27.5)	215 (6.1)	176 (5.0)	0.132	897 (23.1)	182 (4.7)	372 (9.6)	78 (2.0)	0.027
25.0–29.9	741 (18.2)	392 (9.7)		741 (21.1)	138 (3.9)	106 (3.0)		686 (17.7)	118 (3.0)	242 (6.2)	39 (1.0)	
≥30 (obese)	512 (12.6)	297 (7.3)		512 (14.5)	114 (3.2)	76 (2.2)		484 (12.5)	102 (2.6)	152 (3.9)	31 (0.8)	
Current Smoking												
No	1854 (45.6)	1059 (26.1)	0.065	1854 (52.7)	359 (10.2)	302 (8.6)	0.009	1733 (44.6)	324 (8.3)	630 (16.2)	118 (3.0)	0.527
Yes	695 (17.1)	453 (11.2)		695 (19.7)	183 (5.2)	126 (3.6)		641 (16.5)	131 (3.4)	263 (6.8)	44 (1.1)	
Diabetes^{§§}												
No	2513 (61.9)	1489 (36.7)	0.787	2513 (71.4)	537 (15.3)	421 (12.0)	0.587	2340 (60.2)	447 (11.5)	879 (22.6)	157 (4.0)	0.423
Any	36 (0.9)	23 (0.5)		36 (1.0)	<10 (<0.3)	<10 (<0.3)		34 (0.9)	<10 (<0.3)	14 (0.4)	<10 (<0.3)	
Hypertension^{**}												
No	2342 (57.7)	1409 (34.7)	0.142	2342 (66.5)	511 (14.5)	391 (11.1)	0.132	2175 (56.0)	422 (10.9)	829 (21.3)	152 (3.9)	0.503
Yes	207 (5.1)	103 (2.5)		207 (5.9)	31 (0.9)	37 (1.1)		199 (5.1)	33 (0.9)	64 (1.6)	10 (0.3)	
HPV vaccination status^{§††}												
Unvaccinated	1277 (36.1)	561 (15.8)		1277 (38.7)	353 (10.7)	208 (6.3)		1194 (35.9)	174 (5.2)	265 (8.0)	61 (1.8)	
Vaccinated	302 (8.5)	193 (5.5)		302 (9.1)	76 (2.3)	117 (3.5)		287 (8.6)	62 (1.9)	60 (1.8)	<10 (<0.3)	
Too old	762 (21.5)	446 (12.6)	<0.001	762 (23.1)	110 (3.3)	99 (3.0)	<0.001	718 (21.6)	166 (5.0)	239 (7.2)	98 (2.9)	<0.001

* The HPV viral/pathology parameters are not independent, so each woman has information for each parameter. Criteria for classifications for all HPV parameters are given in methods and Table 1.

† Maternal characteristics used imputed data.

‡ The age cut off of 20 years was chosen because all of those who were eligible for vaccination were under 25 years of age.

\$ Some groups contained numbers of women of <10 so were not released from the Safe Haven.

Scottish Index of Material Deprivation (SIMD) quintiles were combined as most deprived (quintiles 1&2) vs. least deprived (quintiles 3-5).

Body mass index (BMI, kgm^{-2}) was calculated as weight (kg) divided by the square of the patient's height (m)

Diabetes includes gestational diabetes and pre-existing diabetes (Table 1).

***Hypertension did not distinguish between pre-existing or gestational hypertension within SMR02 (Table 1).

Due to missing data, numbers for the HPV vaccination data do not add up to the totals given.

outcomes from 5,626 women (Figure 1). Of these, 32 were stillbirths, which, although these had been pre-defined as one of the pregnancy outcomes for investigation, were too few for any meaningful analysis and were excluded. For the women who had had more than one pregnancy, we chose the pregnancy nearest the cytology date. The final cohort consisted of 5,598 women.

Women had had term live births (≥ 37 weeks gestation, $n=4942$, 88.3%); all preterm birth (<37 weeks gestation, $n=386$, 6.9% [including those who had a late miscarriage, $n=26$]) and early miscarriage (<13 weeks gestation, $n=270$, 4.8% [obtained from SMR02, $n=156$, and SMR01, $n=114$]). On comparison with Scottish birth statistics²³, the age distribution of the cohort was much younger than that of the Scottish childbearing population. There were more pregnancy outcomes in women of <25 years (62.9%) than in the Scottish population²³ (26.5%) and a smaller proportion of mothers aged 25–34 years (28.8% vs. 53%) or ≥ 35 years (8.3% vs. 20.5%) in our cohort, respectively. The percentage of all women who had a preterm birth in our cohort (6.9%) was similar to that of the Scottish population²³, which ranged between 5.8 and 6.7% (between 1999 and 2015). The percentage of women having hospital admission for early miscarriage in our population was much lower (4.8%) than that in the Scottish birth data²³. Due to this low rate of miscarriage, the miscarriage data were deemed to be problematic due to uncertainty in case ascertainment and was thought to not be representative of the Scottish child-bearing population. Therefore, the results for early miscarriage are not presented.

The characteristics of the women according to the HPV viral/pathology parameters are shown in Table 5 for the whole cohort. The percentage of women with HR HPV-positive results in our cohort was 27.5%, which is higher than the HR-HPV prevalence (18%) seen previously in the Scottish screening population²⁸, probably due to the nature of 'selective' sampling in the Scottish HPV Archive. Similarly, the percentage of women with HPV-16/18 was higher than that in the routine prevalence in the same population (9.7% vs. 2.9%, respectively). For HPV-associated disease, some women were HR HPV-negative or of unknown genotype but showed evidence of HPV-associated disease. The proportion of women with low-grade disease was higher in our cohort than in the national screening data (16.0% vs. 7.5%, respectively) and our cohort had a higher percentage of women with high-grade cervical disease (2.9% vs. 1%, respectively).

Analysis of the cohort

The numbers and percentages for the maternal factors were compared by pregnancy outcomes (term live births vs. all preterm birth, Table 4). There were no significant differences in maternal age, ethnicity, parity, SIMD (most vs. least deprived), BMI or hypertension between women who had term live births compared with those who had preterm births. A higher proportion of all women who had a preterm birth were current smokers when compared with those who had term live births ($P<0.001$). Similarly, a higher proportion of all women who had a preterm birth also had diabetes than those who had term live birth ($P=0.063$, Table 4).

The numbers and percentages of women in each analysis and the unadjusted and adjusted OR from binary logistic regression are shown for each HPV viral/pathology parameter and all women who had a preterm birth, for all women (Table 6) and vaccine-eligible women (Table 7); similarly results for spontaneous preterm birth are shown in Table 8 and Table 9.

HR HPV. Binary logistic regression showed that women who carried any HR HPV had increased odds of having a preterm birth in unadjusted models, but the association was lost in adjusted models (Table 6). In vaccine-eligible women there was no association between HR HPV and all preterm birth and no effect of vaccine (Table 7). Similarly, for spontaneous preterm birth, there was no association between HR HPV and spontaneous preterm birth in the whole cohort (Table 8), nor in vaccine-eligible women and no effect of vaccine (Table 9). Current smoking and/or diabetes were independently associated with increased odds of all preterm birth and/or spontaneous preterm birth. Hypertension was an independent predictor of all preterm birth in all women but not vaccine-eligible women.

HR HPV 16/18 types. Only 970 women had known specific HR HPV types. There were no associations between carriage of HPV16/18 types or non16/non18 HPV types and all preterm birth (Table 6 and Table 7) or spontaneous preterm birth (Table 8 and Table 9) in the whole cohort nor in vaccine-eligible women, and vaccination had no effect. Current smoking and/or diabetes were independently associated with increased odds of any and/or spontaneous preterm birth. Hypertension was an independent predictor of any preterm birth in all women but not vaccine-eligible women.

HPV-associated cervical disease. In the whole cohort of women, high-grade cervical disease was significantly associated with $\sim 80\%$ increased odds of any and spontaneous preterm birth (Table 6 and Table 8, respectively) in unadjusted and adjusted models of all women. In the vaccine-eligible women there were no associations between any level of HPV-associated disease and no effect of vaccination in any preterm birth or spontaneous preterm birth (Table 7 and Table 9, respectively). Current smoking and diabetes were also associated with an increased odds of any or spontaneous preterm birth in all women. Younger maternal age showed a decreased association with HPV-associated cervical disease in the models for both any and spontaneous preterm birth.

Discussion

This study found associations between different HPV viral/pathology parameters and adverse pregnancy outcomes. Specifically, high-grade HPV-associated cervical disease was associated with preterm birth and spontaneous preterm birth in the whole cohort women, but not in the vaccine-eligible subgroup of younger women. No associations were seen between HR HPV-positive (with no disease) or low-grade HPV-associated cervical disease and all or spontaneous preterm birth.

Associations between high-grade cervical disease and all preterm birth or spontaneous preterm birth have been suggested in

Table 6. Any preterm birth compared with term live-birth in all women, according to HPV viral/pathological parameters. Table shows the pregnancy outcomes: term live births (>37 weeks gestation) and any preterm birth (<37 weeks gestation) compared by each HPV parameter for all women in the cohort. The numbers and percentages in each group are shown. The odds ratios (OR) and P values from unadjusted and adjusted binary logistic regression models are shown. Significant associations are highlighted in bold.

HPV Parameter	Term live birth, n (%) [*]	Any preterm birth, n (%) [*]	Results from logistic regression models	
			Unadjusted OR (95% CI) p value	Adjusted † OR (95% CI) p value
HR HPV				
Negative	2281 (93.3)	165 (6.7)	Reference	Reference
Positive	1302 (91.4)	122 (8.6)	1.295 (1.015–1.653) 0.037	1.260 (0.985–1.612) 0.066
HPV16/18 type				
HR Negative	2281 (93.3)	165 (6.7)	Reference	Reference
HPV16/18	471 (91.5)	44 (8.5)	1.291 (0.913–1.827) 0.149	1.255 (0.883–1.784) 0.205
Non16/non18 HR HPV	369 (91.8)	33 (8.2)	1.236 (0.837–1.825) 0.286	1.174 (0.792–1.740) 0.424
HPV-associated cervical disease ‡				
HR negative	2123 (93.3)	153 (6.7)	Reference	Reference
HR HPV+ve no disease	387 (92.4)	32 (7.6)	1.147 (0.772–1.702) 0.496	1.110 (0.745–1.655) 0.608
Low-grade abnormalities	773 (92.7)	61 (7.3)	1.095 (0.805–1.490) 0.564	1.061 (0.777–1.448) 0.710
High-grade disease	140 (88.1)	19 (11.9)	1.883 (1.135–3.125) 0.014	1.843 (1.101–3.083) 0.020

^{*} Due to missing HPV data, numbers and percentages relate to the numbers that were present in each analysis and do not add up to the total numbers of women in each pregnancy outcome.

[†] Adjusted binary logistic regression models used the imputed dataset and are pooled results from 5 imputations. Models were adjusted for ethnicity, SIMD (most deprived vs. least deprived), maternal age, parity, smoker in current pregnancy, diabetes, hypertensive disorder and maternal BMI.

[‡] Criteria for HPV-associated cervical disease are shown in the methods and Table 1.

Cofactors that had a significant association with preterm birth from these models were:

HR HPV: Current Smoking OR=1.429 (1.096–1.863) P=0.008; Diabetes OR=2.745 (1.280–5.884) P=0.010; Hypertension OR=1.552 (1.045–2.305) P=0.030.

HR HPV16/18 type: Current Smoking OR=1.367 (1.018–1.836) P=0.038; Diabetes OR=3.243 (1.414–7.441) P=0.006; Hypertension OR=1.609 (1.051–2.462) P=0.029.

HPV-associated cervical disease: Current Smoking OR=1.573 (1.193–2.073) P=0.001; Diabetes OR=2.641 (1.271–5.489) P=0.009; Maternal age ≤20 years OR=0.686 (0.495–0.950) P=0.023.

previous studies^{13,14}. In this study, such associations were not seen in the younger, vaccine-eligible subgroup of women, suggesting that the older women were infected for longer and had time to develop high-grade cervical disease³⁰. Previous studies showing associations between HPV-associated cervical disease and preterm birth have been ambiguous regarding whether these were due to HPV-infection itself, development of associated CIN lesions or the excision of these lesions^{31,32}. Low-grade cervical lesions are more likely to be associated with productive HPV-infections, where the viral life-cycle is completed, compared with infections associated with severe disease where the viral life-cycle is poorly supported³³. Productive infections are also associated with a peak/burst of viral load over a narrower time-frame than infections associated with high-grade disease³⁴. Therefore, in the absence of any associations with HR HPV-infection alone or low-grade cervical disease, and given that over 90% of those who had high-grade disease would have been treated⁴, we suggest that the association with high-grade

cervical disease, in our cohort, is likely to be due to the treatment of HPV-associated cervical disease rather than a direct effect of HPV-infection itself. The clinical implication is that women who have undergone treatment for HPV-associated cervical disease should be closely monitored in subsequent pregnancies for any signs of preterm birth.

Although only HPV-associated high-grade cervical disease was associated with all preterm birth and spontaneous preterm birth, current smoking was consistently associated with spontaneous preterm birth. Smoking is a previously recognised risk factor for spontaneous preterm birth³⁵. Diabetes and hypertension were also independently associated with all preterm birth, but this was not surprising as these are likely to be the indicative reasons for early delivery of the baby. A recent study suggested that HPV infection in the placenta was associated with a number of pregnancy complications³⁶, including gestational diabetes. However, our data did not find an increased associa-

Table 7. Any preterm birth compared with term live-births in vaccine-eligible women, according to HPV viral/pathological parameters. Table shows the women with each pregnancy outcome: term live births (>37 weeks gestation) and any preterm birth (<37 weeks gestation) compared by each HPV parameter for vaccine-eligible women in the cohort. The numbers and percentages in each group are shown. The odds ratios (OR) and P values from unadjusted and adjusted binary logistic regression models are shown. Significant associations are highlighted in bold.

HPV Parameter	Term live birth*, n (%)	Any preterm birth*, n (%)	Results from logistic regression	
			Unadjusted OR (95% CI) p value	Adjusted † OR (95% CI) p value
HR HPV				
HR HPV negative	1583 (93.2)	115 (6.8)	Reference	Reference
HR HPV Positive	905 (91.2)	87 (8.8)	1.323 (0.990–1.769) 0.059	1.282 (0.956–1.719) 0.098
With adjustment for Vaccination status				
HR HPV negative	1583 (93.2)	115 (6.8)	Reference	Reference
HR HPV Positive	905 (91.2)	87 (8.8)	1.310 (0.943–1.820) 0.108	1.255 (0.899–1.752) 0.182
Unvaccinated	2026 (92.6)	163 (7.4)	Reference	Reference
Vaccinated	510 (93.4)	36 (6.6)	0.884 (0.591–1.320) 0.545	0.925 (0.613–1.395) 0.710
HPV16/18 type				
HR HPV negative	1583 (93.2)	115 (6.8)	Reference	Reference
HR HP16/18	371 (91.2)	36 (8.8)	1.336 (0.903–1.975) 0.147	1.312 (0.883–1.948) 0.179
Non-16/non18 HR HPV	280 (91.2)	27 (8.8)	1.327 (0.857–2.057) 0.205	1.247 (0.801–1.943) 0.328
With adjustment for Vaccination status				
HR negative	1583 (93.2)	115 (6.8)	Reference	Reference
HPV 16/18	371 (91.2)	36 (8.8)	1.282 (0.859–1.912) 0.224	1.252 (0.836–1.875) 0.276
Non16/non18 HR HPV	280 (91.2)	27 (8.8)	1.349 (0.863–2.109) 0.188	1.260 (0.801–1.982) 0.318
Unvaccinated	2026 (92.6)	163 (7.4)	Reference	Reference
Vaccinated	510 (93.4)	36 (6.6)	0.879 (0.587–1.317) 0.533	0.925 (0.611–1.399) 0.710
HPV-associated Cervical Disease‡§				
HR negative	1464 (93.2)	107 (6.8)	Reference	Reference
HR HPV+ve no disease	236 (91.5)	22 (8.5)	1.275 (0.790–2.059) 0.319	1.251 (0.772–2.029) 0.363
Low-grade abnormalities	561 (93.0)	42 (7.0)	1.024 (0.708–1.483) 0.899	0.980 (0.674–1.426) 0.918
High-grade disease	-- (89.0)	-- (11.0)	1.710 (0.761–3.844) 0.194	1.577 (0.693–3.586) 0.277
With adjustment for Vaccination status				
HR negative	1464 (93.2)	107 (6.8)	Reference	Reference
HR HPV+ve no disease	236 (91.5)	22 (8.5)	1.275 (0.754–2.158) 0.365	1.223 (0.718–2.084) 0.458
Low-grade abnormalities	561 (93.0)	42 (7.0)	0.989 (0.600–1.629) 0.965	0.935 (0.564–1.549) 0.793
High-grade disease	-- (89.0)	-- (11.0)	1.673 (0.741–3.799) 0.216	1.506 (0.655–3.463) 0.335
Unvaccinated	2026 (92.6)	163 (7.4)	Reference	Reference
Vaccinated	510 (93.4)	36 (6.6)	0.823 (0.518–1.308) 0.410	0.863 (0.538–1.386) 0.543

* Due to missing HPV data, numbers and percentages relate to the numbers that were present in each analysis and do not add up to the total numbers in each pregnancy outcome.

† Adjusted binary logistic regression models used the imputed dataset and are pooled results from 5 imputations. Models were adjusted for ethnicity, SIMD (most deprived vs. least deprived), maternal age, parity, smoker in current pregnancy, diabetes, hypertensive disorder and maternal BMI.

‡ Criteria for HPV-associated cervical disease are shown in the methods and Table 1.

§ Where there were groups containing <10 women, the numbers were not released from the Safe Haven and only the percentages are given.

Cofactors that had a significant association with preterm birth from these models were:

HR HPV: without adjustment for vaccination Diabetes OR=3.552 (1.495–8.442), P=0.004; with adjustment for vaccination Diabetes OR=4.479 (1.834–10.94) P=0.001.

HR HPV16/18 type: without adjustment for vaccination Diabetes OR=4.158 (1.714–10.09) P=0.002; with adjustment vaccination Diabetes OR=4.478 (1.832–10.95) P=0.001.

HPV-associated cervical disease: without adjustment for vaccination Diabetes OR=3.529 (1.479–8.422) P=0.004; with adjustment for vaccination Diabetes OR=4.992 (1.999–12.46) P=0.001, Maternal age ≤20 years OR=0.669 (0.448–0.998) P=0.049.

Table 8. Spontaneous preterm birth compared with term live-birth in all women, according to HPV viral/pathological parameters.

Table shows the women who had pregnancy outcomes: term live births (>37 weeks gestation) and spontaneous preterm birth (<37 weeks gestation) compared by each HPV parameter for all women. The numbers and percentages in each group are shown. The odds ratios (OR) and P values from unadjusted and adjusted binary logistic regression models are shown. Significant associations are highlighted in bold.

HPV Parameter	Term live birth, n (%) [*]	Any preterm birth, n (%) [*]	Results from logistic regression models	
			Unadjusted OR (95% CI) p value	Adjusted † OR (95% CI) p value
HR HPV				
Negative	2281 (94.2)	140 (5.8)	Reference	Reference
Positive	1302 (93.0)	98 (7.0)	1.226 (0.939–1.602) 0.134	1.189 (0.908–1.556) 0.209
HPV16/18 type				
HR Negative	2281 (94.2)	140 (5.8)	Reference	Reference
HPV16/18	471 (93.1)	35 (6.9)	1.291 (0.825–1.777) 0.328	1.169 (0.794–1.723) 0.429
Non16/non18 HR HPV	369 (92.7)	29 (7.3)	1.280 (0.846–1.939) 0.243	1.220 (0.803–1.854) 0.352
HPV-associated cervical disease ‡				
HR negative	2123 (94.2)	130 (5.8)	Reference	Reference
HR HPV+ve no disease	387 (93.3)	28 (6.7)	1.182 (0.774–1.803) 0.439	1.141 (0.746–1.746) 0.544
Low-grade abnormalities	773 (93.9)	50 (6.1)	1.056 (0.755–1.479) 0.750	1.015 (0.723–1.426) 0.930
High-grade disease	140 (89.7)	16 (10.3)	1.866 (1.080–3.224) 0.025	1.791 (1.028–3.121) 0.040

^{*} Due to missing HPV data, numbers and percentages relate to the numbers that were present in each analysis and do not add up to the total numbers in each pregnancy outcome.

[†] Adjusted binary logistic regression models used the imputed dataset and are pooled results from 5 imputations. Models were adjusted for ethnicity, SIMD (most deprived vs. least deprived), maternal age, parity, smoker in current pregnancy, diabetes, hypertensive disorder and maternal BMI. Any cofactors that had a significant association with preterm birth from these models are shown.

[‡] Criteria for HPV-associated cervical disease are shown in the methods.

Cofactors that had a significant association with preterm birth from these models were:

HR HPV: Current smoking OR=1.448 (1.079–1.942), P=0.014

HR HPV16/18 type: Current Smoking OR=1.445 (1.050–1.990), P=0.024

HPV-associated cervical disease: Current Smoking OR=1.599 (1.182–2.162) P=0.002; Diabetes OR=2.499 (1.088–5.738) P=0.031; Maternal Age ≤20 years OR=0.662 (0.464–0.945) P=0.023.

Table 9. Spontaneous preterm birth compared with term live-births in vaccine-eligible women, according to HPV viral/pathological parameters.

Table shows the pregnancy outcomes term live births (>37 weeks gestation) and spontaneous preterm birth (<37 weeks gestation) compared by each HPV parameter for vaccine-eligible women. The numbers and percentages in each group are shown. The odds ratios (OR) and P values from unadjusted and adjusted binary logistic regression models are shown. Significant associations are highlighted in bold.

HPV Parameter	Term live birth [*] , n (%)	Any preterm birth [*] , n (%)	Results from logistic regression	
			Unadjusted OR (95% CI) p value	Adjusted † OR (95% CI) p value
HR HPV				
HR HPV negative	1583 (94.3)	95 (5.7)	Reference	Reference
HR HPV Positive	905 (93.0)	68 (7.0)	1.252 (0.907–1.727) 0.171	1.210 (0.874–1.674) 0.251
<i>With adjustment for Vaccination status</i>				
HR HPV negative	1583 (94.3)	95 (5.7)	Reference	Reference
HR HPV Positive	905 (93.0)	68 (7.0)	1.300 (0.908–1.862) 0.151	1.256 (0.874–1.806) 0.218
Unvaccinated	2026 (93.5)	140 (6.5)	Reference	Reference
Vaccinated	510 (95.1)	26 (4.9)	0.740 (0.467–1.174) 0.202	0.756 (0.472–1.211) 0.244

HPV Parameter	Term live birth*, n (%)	Any preterm birth*, n (%)	Results from logistic regression	
			Unadjusted OR (95% CI) p value	Adjusted † OR (95% CI) p value
HPV16/18 type				
HR HPV negative	1583 (94.3)	95 (5.7)	Reference	Reference
HR HP16/18	371 (93.0)	28 (7.0)	1.258 (0.813–1.946) 0.303	1.230 (0.792–1.910) 0.358
Non-16/non18 HR HPV	280 (92.1)	24 (7.9)	1.428 (0.897–2.275) 0.133	1.348 (0.843–2.155) 0.213
With adjustment for Vaccination status				
HR negative	1583 (94.3)	95 (5.7)	Reference	Reference
HPV 16/18	371 (93.0)	28 (7.0)	1.179 (0.754–1.843) 0.470	1.156 (0.737–1.814) 0.528
Non16/non18 HR HPV	280 (92.1)	24 (7.9)	1.474 (0.917–2.370) 0.109	1.396 (0.864–2.256) 0.173
Unvaccinated	2026 (93.5)	140 (6.5)	Reference	Reference
Vaccinated	510 (95.1)	26 (4.9)	0.725 (0.455–1.154) 0.175	0.742 (0.461–1.193) 0.218
HPV-associated Cervical Disease ‡ §				
HR negative	1464 (94.3)	88 (5.7)	Reference	Reference
HR HPV+ve no disease	236 (92.5)	19 (7.5)	1.339 (0.801–2.241) 0.266	1.319 (0.785–2.216) 0.295
Low-grade abnormalities	561 (94.3)	34 (5.7)	1.008 (0.671–1.516) 0.968	0.959 (0.635–1.449) 0.843
High-grade disease	-- (90.3)	-- (9.7)	1.782 (0.748–4.250) 0.192	1.625 (0.673–3.922) 0.280
With adjustment for Vaccination status				
HR negative	1464 (94.3)	88 (5.7)	Reference	Reference
HR HPV+ve no disease	236 (92.5)	19 (7.5)	1.372 (0.785–2.397) 0.267	1.326 (0.755–2.330) 0.327
Low-grade abnormalities	561 (94.3)	34 (5.7)	1.126 (0.671–1.888) 0.654	1.066 (0.632–1.798) 0.812
High-grade disease	-- (90.3)	-- (9.7)	1.687 (1.704–4.041) 0.241	1.518 (0.622–3.701) 0.359
Unvaccinated	2026 (93.5)	140 (6.5)	Reference	Reference
Vaccinated	510 (95.1)	26 (4.9)	0.689 (0.407–1.168) 0.167	0.719 (0.420–1.231) 0.229

* Due to missing HPV data, numbers and percentages relate to the numbers that were present in each analysis and do not add up to the total numbers in each pregnancy outcome.

† Adjusted binary logistic regression models used the imputed dataset and are pooled results from 5 imputations. Models were adjusted for ethnicity, SIMD (most deprived vs. least deprived), maternal age, parity, smoker in current pregnancy, diabetes, hypertensive disorder and maternal BMI. Any cofactors that had a significant association with preterm birth from these models are shown.

‡ Criteria for HPV-associated cervical disease are shown in the methods.

§ Where there were groups containing <10 women, the numbers were not released from the Safe Haven and only the percentages are given.

Cofactors that had a significant association with preterm birth from these models were:

HR HPV: without adjustment for vaccination status there were no significant cofactors; with adjustment for vaccination status Diabetes OR=3.190 (1.054–9.652) P=0.040

HR HPV16/18 type: without adjustment for vaccination status there were no significant cofactors; with adjustment for vaccination status Diabetes OR=3.165 (1.045–9.586), P=0.042.

HPV-associated cervical disease: without adjustment for vaccination Diabetes OR=3.113 (1.146–8.456) P=0.026; with adjustment for vaccination status Diabetes OR=4.270 (1.513–12.05) P=0.006

tion between HPV viral/pathology data and diabetes and so do not support such an association.

There are strengths and weaknesses for this study. The strengths of this study are that this was a data linkage study starting with women for whom HPV-infection status was known. The use

of the Scottish HPV Archive meant that the HPV viral/pathology parameters for these women had been robustly characterised and the HPV information was not available from any other source. The use of routinely collected data should also reduce bias in the recording of clinical information. Primary HPV screening in Scotland will soon include results from HPV testing. Such

information may facilitate a future population-wide analysis of the effects of HPV-infection and pregnancy outcomes in the Scottish population.

A weakness of the study is that we did not have details of any treatments for cervical disease, so we have had to rely on an assumption that women with high-grade disease received excisional treatment as per national guidelines. The age-distribution of the women did not reflect that of the Scottish childbearing population²³, and therefore, it is hard to determine how representative these results are of the wider population. The study cohort was drawn from the general population by the fact that they underwent cervical screening, but were considerably younger at pregnancy outcome and had higher proportions of women with HPV-infection and HPV-associated cervical disease, due to the selective nature of the samples within the Scottish HPV Archive. The preterm birth rates were similar to that in the Scottish population. The early miscarriage data were obtained from maternity/hospital admission records, but would not include miscarriages managed at home, through outpatient and emergency departments or by General Practitioners. The risk of miscarriage increases with age, particularly after the age of 40 years, although a slightly increased risk of miscarriage exists in women aged under 20 years³⁸. The miscarriage rate in our population was much lower than the that reported for miscarriages managed in hospitals²³. While this lower rate may particularly reflect the youth of our cohort, the differences are hard to explain, and so these data were not presented.

In summary, our data linkage study has found no evidence that HPV infection per se, or low-grade HPV-associated cervical disease was associated with preterm birth. High-grade disease, the majority of which is treated with excisional treatments, was associated with spontaneous preterm birth. This is consistent with previous evidence linking excisional cervical treatment with increased risk of spontaneous preterm birth¹³.

Data availability

Underlying data

The linked dataset was analysed within the NHS National Safe Haven, provided by NHS Research Scotland. The Safe Haven

is a remote server through which the researcher accesses the health data and services to enable research while protecting the confidentiality of the data. Data remains under the control of the NHS and complies with legislative and NHS policies. The linked dataset is archived within the Safe Haven and is available by application to NHS Scotland via the electronic Data Research and Innovation Service (eDRIS), within NHS National Services Scotland (<https://www.isdscotland.org/Products-and-Services/eDRIS/>).

To apply for access to these data, please read the [guide for researchers](#) and then complete the [Enquiry Form](#), describing your planned study and the data required, and email it to nss.edris@nhs.net.

Reporting guidelines

Figshare: RECORD checklist for “HPV infection and pre-term birth: a data-linkage study using Scottish Health Data”. <https://doi.org/10.6084/m9.figshare.7764755.v1>³⁹.

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We acknowledge the help of the eDRIS team, based at the Farr Institute for Health Informatics Research, for facilitating the data-linkage, for providing access to and maintenance of the Safe Haven for the analysis.

Parts of this study have been previously presented at the Scottish Investigator’s Network meeting (SHINe), Edinburgh, UK (June 2017) and the Scottish Colposcopy Meeting, Dunfermline, UK (September 2017).

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Open Peer Review

Current Peer Review Status:   

Version 1

Reviewer Report 29 March 2019

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Fay Crawford

Queen Margaret Hospital, NHS Fife, Dunfermline, UK

This data linkage study has analysed data for associations between HPV infections and/or HPV-associated cervical disease and pre-term birth.

The researchers included data from a Scottish population of 5,626 women who are not entirely representative of the Scottish childbearing population. However, this and other weaknesses of the study are candidly discussed.

The finding that poor maternal outcomes are not associated with HPV infection but high-grade cervical disease converges with other studies on the subject but is interesting and important to report in this data registry population.

The association between smoking, diabetes and hypertension and poor pregnancy are known but it is useful to have these results added to the evidence base.

The paper is very well-written and clear.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health services research, evidence based health care, observational study design and analysis.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 25 March 2019

<https://doi.org/10.21956/wellcomeopenres.16519.r35031>

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Ronnie Lamont 

Department of Obstetrics and Gynaecology, University College London (UCL), London, UK

Originality:

I am not aware of any similar registry based study.

Clinical importance:

Preterm birth (PTB) is an important area of research because it is the major cause of neonatal mortality and morbidity worldwide, and infection is a major cause, particularly at low gestational ages.

Scientific merit:

I am not qualified to comment on the use of registry data, the statistical methods in general or the use of imputation techniques in particular. Otherwise I have no problem with the conduct or methodology of the study.

Comments

1. Bearing in mind the paucity of research in this area, the authors should consider citing the review of adverse outcomes of pregnancy in association with HPV (*Bonde U, et al.* The potential role of HPV vaccination in the prevention of infectious complications of pregnancy¹).
2. The authors should consider alluding to the safety or otherwise of HPV vaccination in pregnancy (*Bonde U, et al.* Is HPV vaccination in pregnancy safe?²).
3. The study by Bruinsma (cited as Reference 14) had significant flaws and these were highlighted in the subsequent correspondence (Lamont RF, Sarhanis P. Precancerous changes in the cervix and risk of subsequent preterm birth³). This should be mentioned.

4. Although well defined in the main text, the term “cervical disease” is nebulous in the context of the abstract. If the word count permits, it would be worth making this clearer in the abstract.
5. I had to search for the definition of “vaccine eligible” and found this in the last part of Table 1. To appreciate the importance of the 1st two paragraphs of the discussion, it would be helpful for this to be defined in the methods section.
6. I found Table 5 very confusing, particularly with respect to vaccination status compared to HPV viral/pathology parameters. The statistically significant results may need to be spelled out/expanded in the text rather than having to be gleaned from the Table.
7. I had to read the first two paragraphs of the discussion half a dozen times before I understood the message. This might be due to my ignorance and may become more clear once comments 5 and 6 above are addressed, but I think could be made clearer if expanded. There must be better ways of making terms such as “vaccine-eligible sub-group of younger women”, and “productive HPV-infections”, better understood.
8. In the study, the outcome of PTB was a categorical variable. Was it possible to stratify the gestational age of PTB in relation to HR-HPV and cervical disease? In other words, if PTB was considered as a continuous variable was there sufficient data to demonstrate an association between HR-HPV, cervical disease and extreme, early or late PTB?
9. The authors record that current smoking was independently associated with an increased risk of PTB, but did not speculate on the link. One possibility is through temperate phage viruses being provoked to become lytic by cigarette smoke carcinogens in cervicovaginal secretions. Diet acquired phage viruses, may be induced to become lytic by factors related to sexual activity, and *Lactobacillus* phage viruses may be directly inoculated into the vagina from male or female partners. Benzo-(a)-pyrene-dio-epoxide (BPDE), the metabolite of a chemical carcinogen in cigarette smoke, can be found in the vaginal secretions of women who smoke. With increasing concentrations of BPDE, there is an increase in the frequency of phage released. Cigarette smoke chemicals promote phage induction in vaginal lactobacilli, and these phages lyse other vaginal *Lactobacillus* strains. Tobacco products can be found in the cervical secretions of women with CIN and in the semen of smokers. Bacterial vaginosis is more common in women who smoke and both BV and smoking are linked by common sequelae such as PTB. It is therefore possible that female smokers secrete, or their partners who smoke, may introduce, by sexual transmission, tobacco products like BPDE into the vagina, which puts them at greater risk of BV by inducing endogenous or sexually acquired *Lactobacillus* phages to become lytic and an increased the risk of PTB.
10. The clear message to me was, that PTB in association with HPV and CIN, was more likely to be due to the treatment of HR-HPV with HGCIN, than the presence of HR-HPV and HGCIN *per se*. This did not become clear to me until the last sentence of the discussion. Could this be made clearer earlier in the manuscript.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infection and antibiotics i the aetiology, prediction and prevention of preterm birth

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 11 March 2019

<https://doi.org/10.21956/wellcomeopenres.16519.r35032>

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Pierre L. Martin-Hirsch

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This study is an important and timely contribution to the evidence base around the influence of oncogenic HPV subtypes and pre-term labour. It is excellently written. I am not an expert in statistics but the methodology looks fine. Previous reports by Bruinsma cited by the author have suggested that the presence of dysplasia of all types potentially increases the risk of preterm labour whilst there is clear evidence that excisions treatment significantly increases risk particularly if excisions are of excessive volume/depth.

This linkage study from robust databases within the Scottish health care system relating HPV status and pregnancy outcomes is very timely as it clearly demonstrates that having HPV infection alone without treatment does not influence pregnancy outcomes .

There is growing evidence that observational management for low and intermediate grade cervical precursors leads to high rate of spontaneous regression and therefore excisional treatment can be

avoided. Women can have the re-assurance that their risk of adverse pregnancy outcomes is not increased by HPV transient disease. Furthermore, with the advent of primary HPV screening, when significant proportion of women are going to found to be High risk HPV positive but disease free, can also be re-assured by this data that this will not increase the risk of pre-term delivery etc.

I think this study is an important contribution and should be shared with individuals designing information resources for women regarding HPV testing etc.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Colposcopy, cervical screening, meta-analysis

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
